REMARKS

Justification for the amendments is as follows. The amendments were made to further clarify the claims. No new matter is added by any of the above amendments. Attached hereto is a marked-up version of the changes made by the present amendment. The attached page is captioned "Version with markings to show changes made."

I. Rejection under 35 U.S.C. 102(b)

The Examiner maintained the rejection of claims 14 and 15 under 35 U.S.C 102(b) as being anticipated by Grotendorst and Bradham, WO 96/38172. This rejection is respectfully traversed.

In the Office Action mailed 23 May 2001 (Paper No. 12), the Examiner stated that " [t]he '172 patent teaches a method of detecting kidney fibrosis (i.e. a disease caused by overproduction of extracellular matrix) by detecting CTGF and comparing said detection to a standard (page 3 and 7, in particular)." The Examiner stated "the '172 patent [sic] does teach detecting kidney fibrosis by detecting CTGF levels and comparing them to a standard...." (Office Action, page 2, section 4.) Further, the Examiner stated that Applicants' specification teaches that kidney fibrosis is a disease involving proliferation of fibroblast cells and their subsequent production of extracellular matrix.

Applicants maintain that WO 96/38172 relates to methods of diagnosing pathologies characterized by a cell proliferative disorder. Specifically, WO 96/38172 provides a "method of diagnosing pathological states in a subject suspected of having pathology characterized by *a cell proliferative disorder*...." (WO 96/38172, page 3, lines 23 to 25. Emphasis added.) WO 96/38172 defines cell proliferative disorders as "pathological states characterized by the continual multiplication of cells resulting in an overgrowth of a cell population...." (WO 96/38172, page 15, lines 29 to 30.) WO 96/38172 then identifies kidney fibrosis as a disease "in which there is an overgrowth of connective tissue cells". (WO 96/38172, page 7, lines 15 to 17.) In contrast, claim 14 of the instant application is directed to a method of diagnosing "a renal disorder characterized by overproduction of extracellular matrix" in a subject by measuring the levels of CTGF in a sample from the subject. Clearly, cell proliferation and overproduction of extracellular matrix are separate and distinct pathological states that may occur separately, consecutively, or simultaneously within different disorders. As WO 96/38172 does not disclose diagnosing a renal disorder "characterized by overproduction of extracellular matrix" as recited in claims 14 and 15, WO 96/38172 does not anticipate these claims.

As stated above, cell proliferation and overproduction of extracellular matrix are separate and distinct pathological states. Some renal disorders characterized by overproduction of extracellular matrix do not involve cell proliferation. For example, glomerulosclerosis, e.g., associated with diabetic nephropathy, can result in overproduction of extracellular matrix by mesangial cells without cell proliferation. As stated by Del Prete et al. (1998, Nephrol Dial Transplant 13 (Suppl 8):20-25), "progressive expansion of the mesangial matrix, and thickening of the glomerular and tubular basement membranes *without signs of major cell proliferation* are hallmarks of human and experimental diabetic nephropathy." (Abstract. Emphasis added.) WO 96/38172 does not address diagnosis of disorders that do not involve cell proliferation. Thus, WO 96/38172 does not teach measuring CTGF in diagnosis or prognosis of patients with renal disorders that involve overproduction of extracellular matrix, but do not involve cell proliferation.

Further, even in renal disorders characterized by both cell proliferation and overproduction of extracellular matrix, the two phases are pathologically and temporally distinct. For example, both mesangial proliferative glomerulonephritisis and tubulointerstitial fibrosis are characterized by proliferation of mesangial cells or fibroblast cells, respectively, followed by cell differentiation and overproduction of extracellular matrix. Although WO 96/38172 provides for diagnosing the cell proliferative phase of such a renal disorder, the specification does not suggest that CTGF is involved in or diagnostic for the phase associated with overproduction of extracellular matrix. Thus, it would not have been apparent to one of skill in the art to measure CTGF in diagnosis or prognosis of patients with renal disorders in stages of renal dysfunction wherein cell proliferation is not ongoing.

Finally, as previously noted in the amendment filed 23 October 2001 (page 5, section V), the present invention provides the first demonstration that CTGF protein induces renal mesangial cells to produce extracellular matrix. Specifically, CTGF stimulated the production of fibronectin and collagen type I by mesangial cells, without inducing mesangial cell proliferation. (See, Example 1, Figures 1A and 1B.) Similarly, a recent report by Bom et al. (2001, Nephrol Dial Transplant 16:1139-1148) also demonstrated that CTGF protein stimulates fibronectin production, but does not induce proliferation, in mesangial cells. (See, e.g., page 1143, column 2, and page 1144, column 2.) Claim 14 of the instant application is directed to a method of diagnosing "a renal disorder characterized by *overproduction of extracellular matrix.*" (Emphasis added.) WO 96/38172 does not disclose a renal disorder "characterized by overproduction of extracellular matrix" as recited in the instant claims. Therefore, WO 96/38172 does not anticipate these claims.

In summary, WO 96/38172 does not teach a method of diagnosing "a renal disorder characterized by overproduction of extracellular matrix" as recited in claims 14 and 15, and does not anticipate these claims. Withdrawal of the rejection of claims 14 and 15 as being anticipated by this reference under 35 U.S.C. 102(b) is thus respectfully requested.

II. Rejection under 35 U.S.C. 102 (a)

The Examiner maintained the rejection of claims 14 and 15 under 35 U.S.C. 102(a) as being anticipated by Ito et al. (1998, Kidney Int 53:853-861). The Examiner states "the claims are not limited to CTGF protein, just CTGF." (Office Action, page 2, section 5.) The rejection of claims 14 and 15 under 35 U.S.C. 102(a) as anticipated by Ito et al. is respectfully traversed.

Amended claim 14 recites "CTGF protein," as suggested by the Examiner. The amendment was made to clarify the claim, and in no way alters the scope of the claim. Withdrawal of the rejection of claims 14 and 15 as being anticipated under 35 U.S.C. 102(a) by Ito et al. is thus respectfully requested.

III. Rejections under 35 U.S.C. 103

The Examiner maintained the rejection of claim 17 under 35 U.S.C. 103 as being unpatentable over Ito et al. or WO 96/38172. In the previous Office Action dated 23 May 2001, the Examiner stated "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to assay for the presence of CTGF to detect kidney fibrosis as taught by Ito et al., or WO 96/38172, and package the assay as a kit with the expectation that kits allow for ease and commercial reproducibility of known assays." (Paper no. 12, page 4.) The rejection of claim 17 under 35 U.S.C. 103 as being unpatentable over Ito et al. or WO 96/38172 is respectfully traversed.

As stated above, amended claim 14 recites "CTGF protein." As discussed above, Ito et al. showed CTGF mRNA expression in human biopsy specimens, but did not teach or suggest diagnosing a renal disorder using direct measurement of CTGF protein levels in patient samples as in the present invention. Additionally, Ito et al. contains no teaching or suggestion of a diagnostic kit useful for detecting the level of CTGF protein as a method of diagnosing a renal disorder. Therefore, Ito et al. does not in any way teach or suggest the diagnostic kit of claim 17, and claim 17 is thus patentable over Ito.

As stated in the response filed 23 October 2001, WO 96/38172 fails to cure the deficiencies of Ito. As discussed above, the present invention is directed to methods of diagnosing a renal disorder "characterized by overproduction of extracellular matrix," whereas WO 96/38172 relates to methods of

diagnosing pathologies characterized by cell proliferation. Furthermore, as stated above, the present invention provides the first demonstration that CTGF protein induces mesangial cells to produce extracellular matrix. Specifically, CTGF stimulates the production of fibronectin and collagen type I by mesangial cells, without inducing mesangial cell proliferation. (See, Example 1, Figures 1A and 1B.) Additionally, WO 96/38172 contains no teaching or suggestion of a diagnostic kit for diagnosing a renal disorder characterized by overproduction of extracellular matrix. Therefore, WO 96/38172 does not teach or suggest the diagnostic kit of claim 17, and claim 17 is thus patentable over WO 96/38172.

As Ito et al. and WO 96/38172, singly or in combination, do not teach or suggest the diagnostic kit of claim 17, nor provide any motivation for deriving the claimed kit, claim 17 is patentable over both of these references. Withdrawal of the rejection of claim 17 as being unpatentable over these references under 35 U.S.C. 103 is thus respectfully requested.

CONCLUSION

In view of the foregoing, Applicant submits that the claims are fully in condition for allowance and request early notification to that effect. If the Examiner has any questions regarding the present communication or the above-referenced application, please call Applicant's Agent at 650-866-7265.

Applicants believe that no fee is due with this communication. If, however, the Commissioner determines that a fee is due, the Commissioner is hereby authorized to charge any necessary fees to Deposit Account No. **50-0811**. **This form is enclosed in duplicate.**

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claims14 and 17 have been amended as follows:

14. (Thrice Amended) A method for diagnosing a renal disorder characterized by overproduction of extracellular matrix, or identifying a predisposition or susceptibility to a renal disorder characterized by overproduction of extracellular matrix, in a subject, the method comprising:

(a) obtaining a sample from the subject;

(b) detecting the level of CTGF protein in the sample; and

(c) comparing the level of CTGF protein in the sample to a standard level of CTGF protein, wherein increased levels of CTGF protein are indicative of the presence of a renal disorder.

17. (Twice Amended) A diagnostic kit for use in diagnosing a renal disorder characterized by overproduction of extracellular matrix, or identifying a predisposition or susceptibility to a renal disorder characterized by overproduction of extracellular matrix, the method comprising:

(a) a means for detecting the level of CTGF protein in a sample; and

(b) a means for measuring the level of CTGF protein in the sample.